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Improving Outcomes After Stroke By LEAPS (Locomotor Experience Applied Post-Stroke) and Bounds

Steven C. Cramer, MD

Stroke is a chronic, lasting condition. Over 795 000 persons have a new stroke each year.¹ The vast majority survive, with those in the seventh decade living an average of 7 years thereafter,¹ most with some form of loss of function and limitation of activity.² Increasing evidence suggests that these deficits are not fixed, but instead that the brain is plastic, that a number of different therapies have the potential to improve brain structure and function once the acute stroke period passes and stroke injury is fixed, and that this plasticity can reduce post-stroke disability.

Brain plasticity is facilitated by repeated practice. This is true during development, during learning, in times of health, and after brain injury such as stroke. This principle is the foundation of poststroke treatments applied across behavioral modalities such as neglect, aphasia, or weakness. Evidence suggests that the responsiveness of the brain to such intervention declines with time poststroke.³ However, many patients long past stroke can nonetheless benefit from repeated practice such as with an activity-based regimen that is initiated even months after stroke onset. For example, the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial was a landmark study that found that constraint-induced therapy improved upper extremity motor function when initiated 3 to 9 months after stroke onset.⁴

It is in this context that the Locomotor Experience Applied Post-Stroke (LEAPS) trial was initiated. The LEAPS trial focused on improving gait after stroke by comparing 2 different activity-based therapies and 2 different time points. Gait is a priority because it is commonly affected by stroke, gait improvements after stroke are linked to better quality of life,⁵ and hemiplegic patients rank recovery of gait as their top priority.⁶ Importantly, gait velocity is linked to level of social participation.⁷ A typical adult comfortable gait velocity is 3 to 4 mph, or 1.3 to 1.8 m/s. After stroke, a gait velocity that is >0.8 m/s is associated with full community mobility; 0.4 to 0.8 m/s with short walks in the community; and <0.4 m/s with mobility limited to the home. Gait velocity thus has special value as an end point because, in the vernacular of the World Health Organization International Classification of Functioning, Disability and Health, it is a measure of loss of body function that has a clear and direct link to level of participation.

The LEAPS trial was performed at 6 US sites. A total of 4909 patients were screened to enroll 408. Entry criteria included age at least 18 years, living in the community, and <2 months poststroke at the time of randomization. Subjects needed to have leg weakness and a gait velocity <0.8 m/s but be able to walk at least 3 m even if with assistance.

At 2 months after stroke, patients were randomized to 1 of 3 gait training groups: (1) body-weight support treadmill training starting 2 months poststroke; (2) body-weight support treadmill training starting 6 months poststroke; and (3) a progressive home exercise program managed by a physical therapist starting 2 months poststroke. In all cases, training included 36 sessions, 90 minutes in duration, spanning 12 to 16 weeks. Also, for all subjects, the study intervention was in addition to usual care.

The primary outcome was the proportion of participants in each group who at 1 year poststroke had an improvement in functional walking ability, defined as the ability to walk independently at ≥ 0.4 m/s for subjects with initially severe gait impairment or at ≥ 0.8 m/s for subjects with initially moderate gait impairment. Having the end point vary according to baseline status is uncommon in acute stroke trials but seems sensible in restorative stroke trials, in which expectations vary in relation to baseline status and where this approach is more feasible given that a baseline assessment of behavior can be consistently obtained.

Enrollees were well matched at baseline, with mean age 62 years, time poststroke 64 days, 71% confirmed as ischemic stroke, and 99.5% with modified Rankin Scale score 2 to 4. The rate of subject dropout ranged from 3% in Group 3 to 17% in Group 2. Baseline impairment of gait velocity was severe (<0.4 m/s) in just over half of subjects and moderate (0.4 to <0.8 m/s) in the rest. Physical therapy outside study procedures was received by 81.9% of enrollees, who received an average of 25 such sessions.

The primary outcome of transition to a higher functional level of walking 1 year poststroke was achieved by 52% of enrollees with no significant difference among the 3 treatment groups. Secondary end points such as change in gait velocity, distance walked over 6 minutes (gait endurance), and balance also did not differ between groups. Treatments were overall comparable in terms of safety.

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What are some points learned from the LEAPS trial? First, months after stroke onset, when our patients have generally seen their therapy reduced or discontinued, a majority can still experience significant behavioral gains, in this case in a measure that is directly linked with community participation. This is underscored by the study observation that at 6 months after stroke, subjects in Groups 1 and 3, each of whom started study therapy 2 months after stroke, had better scores than subjects in Group 2 who had not yet begun study therapy. An intervention started on the first day poststroke that improved gait velocity in 52% of patients 12 months poststroke would garner great praise; this is no less true when the therapy is initiated weeks after stroke onset.

A second point learned from the LEAPS trial is that initiating study therapy 2 months poststroke had the same long-term effect as initiating therapy 6 months poststroke. It remains to be clarified whether an earlier start would prove superior, for example, if study therapy was initiated in the first month after stroke, a time when the brain is maximally galvanized for plasticity.^{3,8} Third, like in a recent study of robotic therapy for postacute stroke patients,⁹ therapy provided outside of the study procedures complicates interpretation of results. LEAPS was in part a study of usual care plus body-weight support treadmill training versus usual care plus a progressive home exercise program. Usual care was a variable that the study authors could measure but could not control. This issue is difficult to surmount when evaluating postacute stroke therapies, although outside therapy might be more standardized in some countries and in certain practice settings and can be measured and treated as a covariate if desired.¹⁰

The current results are similar to a prior study of subjects with spinal cord injury¹¹ in that the data do not suggest a boost in gains with body-weight support treadmill training. Some might argue that treadmill results might vary with different populations, for example, all LEAPS enrollees had been admitted to an inpatient rehabilitation before enrollment; or with a more intensive training regimen, which might improve outcomes.¹² Nonetheless, the current results support the LEAPS trial authors' conclusion that, as compared with body-weight support treadmill training, "home exercise requires less expensive equipment, its implementation requires a smaller number of staff members, less training is required for physical therapists, and patients are more likely to comply with the regimen."

How might we build on these results? Patients were selected on the basis of behavioral and demographic characteristics, but a baseline measure of brain anatomy or physiology¹³ such as corticospinal tract integrity¹⁴ might prospectively distinguish responders from nonresponders. Behavioral phenotype arises on the basis of many different brain states, but only some brain states are likely to benefit from therapy. Future studies might incorporate measures of brain injury or neurophysiology into entry criteria. Such an approach might reduce variance and so increase power in the clinical trial setting or help maximize the efficiency with which rehabilitation resources are used in the clinical practice setting.

A number of restorative therapies are under study to improve outcomes after stroke. Would behavioral gains in the LEAPS trial have been greater if interventions were accompanied by a pharmacological or cell-based therapy? Future studies might

examine such a proposal, because favorable preclinical and early clinical results exist for a number of candidate therapies.^{15,16}

The LEAPS investigators are to be congratulated for completing a challenging study, over an extended follow-up period, in a cohort that was at a time poststroke that has sometimes received less attention. Sound study design such as matched intensity of intervention across treatment arms and use of an active control group increases the clarity of the message. There was no "nontherapy" control group, and so it is difficult to precisely determine which findings are attributable to usual care alone. LEAPS is 1 of a growing number of studies that relies on modality-specific end points, an approach that may be of particular value for restorative therapies.¹⁷ Overall, LEAPS provides insight into the optimal therapy for improving gait after stroke and reminds us of the enormous potential for brain plasticity that exists in patients beyond the acute phase of stroke.

Disclosures

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References

- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation*. 2010;121:e46–e215.
- Gresham G, Duncan P, Stason W, Adams H, Adelman A, Alexander D, et al. *Post-stroke Rehabilitation*. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1995.
- Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci*. 2004;24:1245–1254.
- Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA*. 2006;296:2095–2104.
- Salbach NM, Mayo NE, Higgins J, Ahmed S, Finch LE, Richards CL. Responsiveness and predictability of gait speed and other disability measures in acute stroke. *Arch Phys Med Rehabil*. 2001;82:1204–1212.
- Bohannon R, Andrews A, Smith M. Rehabilitation goals of patients with hemiplegia. *Int J Rehab Res*. 1988;11:181–183.
- Perry J, Garrett M, Gronley J, Mulroy S. Classification of walking handicap in the stroke population. *Stroke*. 1995;26:982–989.
- Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*. 2008;63:272–287.
- Lo A, Guarino P, Richards L, Haselkorn J, Wittenberg G, Federman D, et al. Robot-assisted rehabilitation for upper extremity impairment in chronic stroke. *N Engl J Med*. 2010;362:1772–1783.
- Cramer SC, Dobkin BH, Noser EA, Rodriguez RW, Enney LA. Randomized, placebo-controlled, double-blind study of ropinirole in chronic stroke. *Stroke*. 2009;40:3034–3038.
- Dobkin B, Apple D, Barbeau H, Basso M, Behrman A, Deforge D, et al. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology*. 2006;66:484–493.
- Kwakkel G. Impact of intensity of practice after stroke: issues for consideration. *Disabil Rehabil*. 2006;28:823–830.
- Nouri S, Cramer S. Anatomy and physiology predict response to motor cortex stimulation after stroke. *Neurology*. 2011;77:1076–1083.
- Riley JD, Le V, Der-Yeghian L, See J, Newton JM, Ward NS, et al. Anatomy of stroke injury predicts gains from therapy. *Stroke*. 2011;42:421–426.
- Cramer SC. Repairing the human brain after stroke. II. Restorative therapies. *Ann Neurol*. 2008;63:549–560.
- Savitz SI, Chopp M, Deans R, Carmichael ST, Phinney D, Wechsler L. Stem cell therapy as an emerging paradigm for stroke (STEPS) II. *Stroke*. 2011;42:825–829.
- Cramer SC, Koroshetz WJ, Finklestein SP. The case for modality-specific outcome measures in clinical trials of stroke recovery-promoting agents. *Stroke*. 2007;38:1393–1395.